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Original Article

Qualitative research and literature review support the integrated Alzheimer's Disease Rating Scale (iADRS) content validity in early symptomatic AD

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ABSTRACT

Background and objectives: The integrated Alzheimer's Disease Rating Scale (iADRS) is a measure of cognition and daily function used to evaluate treatment effects in Alzheimer's disease (AD) clinical trials. This study aimed to assess the content validity of the iADRS in early symptomatic AD, and to determine whether integrating assessment of cognition and function into a single measure of global disease severity is supported by the patients' experience.
Methods: A targeted literature review of qualitative research in AD and qualitative interviews with 25 care partners of individuals with early symptomatic AD were conducted. Interviews started with open-ended concept elicitation exploring the patient experience of AD from the care partner perspective, including how cognitive changes affect daily functioning. This was followed by cognitive debriefing of the ADCS-iADL items. Interview transcripts were analyzed thematically. Concepts extracted from the literature review and interviews were categorized into a conceptual model of patient experience of AD. A concept-to-item mapping exercise was conducted to assess the conceptual coverage of the iADRS.
Results: The literature review comprised sixty articles. Interviews were conducted with care partners of 7 individuals with Mild Cognitive Impairment (MCI)-AD and care partners of 18 individuals with dementia due to AD. The resulting conceptual model incorporated 75 concepts related to AD experience categorized into three overarching domains: Cognition, Daily Function and Other Symptoms/Impacts. Interview findings endorsed the close link between cognition and daily function. Concept-to-item mapping demonstrated all Cognition and Daily function sub-domains within the model were assessed by at least one iADRS item, except Work/Professional, providing supportive evidence that the iADRS covers concepts that reflect the patient experience of early symptomatic AD.
Conclusions: This study offers a comprehensive conceptualisation of the patient experience of early symptomatic AD and highlights the intrinsic connection between cognition and daily function. The findings endorse the relevance of an integrated assessment of cognition and function and provide strong evidence for the content validity of the iADRS, highlighting its utility as a meaningful clinical outcome assessment (COA) for use as an endpoint in AD.

1. Introduction

Alzheimer's Disease (AD) is a neurodegenerative disorder with a complex pathology [1–3]. Clinically, AD is characterized by declines in cognition, function, and behavior that progress over time, ultimately leading to complete dependence and death. Upon first presentation, cognitive impairment may be limited to one or two cognitive domains (episodic memory being most common) but, as the disease progresses, patients with early symptomatic AD, inclusive of Mild Cognitive Impairment (MCI) and mild dementia due to AD (Mild AD), experience declines across multiple cognitive and functional domains. During the early stages of AD, impairment in instrumental activities of daily living (iADL) may occur (e.g., shopping, preparing meals, housework), while basic activities of daily living (bADLs), including tasks like bathing, dressing, toileting [4,5] remain largely intact.

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In recent years, increased understanding of the biological basis for AD and development of biomarkers sensitive to disease pathology (amyloid beta, p-tau) has precipitated development of the first disease modifying treatments for AD. To date, three anti-amyloid treatments (aducanumab, donanemab, and lecanemab) have demonstrated reduced decline on cognitive and functional efficacy endpoints in clinical trials for early symptomatic AD, inclusive of MCI or mild dementia [6–10].

Selection of efficacy endpoints can determine the success of AD clinical trials. As such, careful consideration of relevant endpoint measures is essential to continued success in AD drug development [11]. The integrated Alzheimer's Disease Rating Scale (iADRS) was developed in response to growing awareness that clinical trials targeting early symptomatic stages of AD required primary endpoints with increased sensitivity to clinical decline experienced by individuals with early-stage disease [12]. Developed using both theory and data-driven approaches, the iADRS is an integrated assessment of cognition and daily function comprised of 31 items from two widely accepted measures, the ADAS-Cog$_{13}$ (13 items) [13] and ADCS-iADL (18 items) [14]. The iADRS total score provides a single summary measure of global disease severity across the continuum of AD.

Evidence of the relevance of the conceptual coverage of the iADRS was obtained through the What Matters Most study series [DiBenedetti et al. (2020) [15]; Hauber et al. (2023) [16]; DiBenedetti et al. (2023) [17]). A comprehensive set of 42 concepts (i.e., symptoms, impacts, and treatment-related outcomes) that are meaningful to individuals with AD across the AD continuum were identified through literature and qualitative interviews with individuals with AD and care partners of individuals at varying stages of AD [15,16]. DiBenedetti et al. (2023) [17] evaluated the extent to which these 42 concepts are reflected in COAs commonly used in AD trials. Compared to all other measures, the iADRS demonstrated the most comprehensive coverage of concepts identified as meaningful for individuals across all stages of AD evaluated.

Further evidence from the patient and care partner perspectives on the iADRS is needed to confirm that the conceptual coverage provided by the iADRS is comprehensive in capturing meaningful changes experienced by individuals with early symptomatic AD. Showing that all the important aspects of the patient experience with early AD are reflected in the iADRS is key to appropriately evaluate the effectiveness of treatments and avoid misleading claims. In addition, while the ADAS-Cog$_{13}$ and ADCS-iADL are widely accepted legacy clinical outcome assessments (COAs), used for decades as standalone clinical trial endpoints [17,18], it is important to evaluate the extent to which the patient experience supports combining items from these two scales into a single integrated efficacy endpoint for use in early symptomatic AD.

1.1. Objectives

This study aimed to: (1) conceptualize the patient experience of early symptomatic AD and to cognitively debrief the ADCS-iADL to collect evidence evaluating the content validity of the iADRS in an early symptomatic AD patient population; and (2) explore the relationship between cognition and daily function items to evaluate the appropriateness of integrating the assessment of cognition and daily function into a single measure of global disease severity.

2. Methods

To achieve these goals, a two-step study was conducted comprising a targeted literature review and qualitative interviews with care partners of individuals living with early symptomatic AD. The study was approved by the WCG Institutional Review Board (IRB reference 1,345,864).

2.1. Literature review

A targeted literature review was undertaken in November 2022 using PubMed to identify qualitative research published in the 10 years prior. The review aimed to explore the characteristic symptoms and related impacts experienced by individuals with dementia or MCI due to AD, as reported by individuals with AD and care partners.

Search terms were selected to provide a combination of terms related to the target context of use including mild cognitive impairment, Alzheimer or dementia, and the target methodology (i.e., qualitative, interview, or focus group). Articles were excluded if (i) they did not employ a qualitative methodology; (ii) they did not include participants with MCI or dementia or no care partners of this group; (iii) the etiology was not AD or etiology was not mentioned; (iv) they did not report on concepts related to disease symptom/impact experience (for example experiences of a diagnostic procedure or intervention), (v) they were related systematic reviews or meta-analyses; and (vi) full-text papers were not available in English.

A draft conceptual model was developed based on the findings of the literature review. Standard analytical techniques of conceptual model development were used to conceptualize the concepts identified in the literature [19–21]. Codes and quotations were compared with the rest of the data and inductively categorised into higher-order overarching categories referred to as domains (e.g., cognition; daily function), subdomains (e.g., learning and memory; instrumental ADL) and concepts (e.g., recognition of people; shopping), reflecting their conceptual content underpinning. Data related to cognition were categorized according to DSM-5 cognitive domains [22] of learning and memory, attention, language, executive function, and perceptual-motor.

2.2. Qualitative interviews

2.2.1. Participants

A sample of care partners (target of $n = 25$) from the US were recruited. All care partners provided informed consent and met the following criteria: age ≥ 18 years; frequent contact with an individual with AD (minimum of 10 h direct contact per week); and knowledge, willingness and ability to comment on the individual's cognitive, functional, and emotional state and personal care activities (e.g., bathing, toileting).

The key inclusion criteria for the individuals with AD were: 55–85 years in age; confirmed clinical diagnosis of MCI or dementia due to AD; score ≥20 on the Mini-Mental State Examination (MMSE) or ≥13 on the Montreal Cognitive Assessment (MoCA) within the past 6 months. Care partners were excluded if the individual they care for had comorbid significant neurological disease affecting the central nervous system (other than AD). The individual with AD provided consent to share medical records confirming their clinical diagnosis and cognitive test scores.

Target recruitment quotas for age, sex, ethnicity, education and AD severity were used to identify a sample representative of the patient population. These included a minimum of 6 individuals with AD aged 55–64, 13 individuals with AD aged 65–74 and 6 individuals aged 75–85; 5 male individuals with AD; 3 individuals with AD of a non-white ethnic group; 3 individuals with AD without a college degree, 3 individuals with AD with a college degree; 6 individuals with AD with a score of 20–23 (MMSE) or 13–17 (MoCA), 13 individuals with AD with a score of 24–27 (MMSE) or 18–23 (MoCA), and 6 individuals with AD with score of 28–30 (MMSE) or 24–30 (MoCA).

2.2.2. Interview conduct

One-on-one interviews were conducted via online videoconference with each care partner. Interviews lasted approximately 90-min and were supported by semi-structured interview guides comprised of two sections: (i) concept elicitation to explore symptoms and impacts experienced by the individual with early symptomatic AD and to understand the impact of cognitive changes on daily functioning, designed to elicit both spontaneous and probed information and (ii) cognitive debriefing of the ADCS-iADL to explore the perceived relationship between the activities of daily living assessed by the scale and cognitive impairment, as well as any potential issues concerning ease of completion, relevance, and clarity of the ADCS-iADL items. The ADCS-iADL [14] consists of 18 items completed through an interview-based assessment with care partners to assess the independence of individuals with AD with activities like using the telephone and keeping appointments. During this section of the interview, the items were shared on screen. A "think-aloud" process [23–25] was used to understand the care partners' thought process when selecting responses and whether cognitive impairment was considered the sole factor impacting the activity, as well as what cognitive domains they thought were involved with each activity.

2.3. Qualitative analysis

De-identified transcripts were analyzed thematically [20] through detailed line-by-line inductive and deductive coding [19,26] using ATLAS.ti software [27]. To ensure consistency in coding, independent parallel coding was performed on the first two transcripts and a common codebook was developed for use in subsequent interviews. The coding and analysis was conducted by trained qualitative researchers and synthesis overseen by researches with cognition and neuropsychology expertise.

Concept elicitation coding focused on symptoms and impacts due to AD, and the relationship between cognition and functioning. Once coding was complete, the draft conceptual model based on the literature review findings was synthesized with the data from care partner interviews to develop a consolidated conceptual model of the patient experience of AD across the continuum. Established methods for developing conceptual models [19–21] were used to conceptualize the concepts raised by the care partners. Additionally, the data related to cognition were categorized according to DSM-5 cognitive domains [22]. Saturation analysis was conducted by splitting the transcripts chronologically in five groups of 5 interview transcripts.

Cognitive debriefing coding included multiple-level codes, containing information on the corresponding item/response and the corresponding issue (e.g., clarity/relevance/response option issue). Additional open coding captured care partners' examples of difficulties experienced by the individual with AD for each ADCS-iADL item and the cognitive domains they believed were involved. The research team then analysed these specific difficulties and assigned them with the cognitive sub-domain(s)/concept(s) from the conceptual model thought to be involved.

2.4. Concept-to-item mapping

A descriptive concept-to-item mapping exercise was conducted to assess the conceptual coverage of the iADRS. Each concept included in the conceptual model was compared with the iADRS items to infer the extent to which the iADRS covers concepts meaningful to individuals with AD and identify any potential gaps in its coverage. Considering the concept-to-item mapping is a qualitative descriptive exercise, a multiple sources approach was adopted where mapping was conducted and synthesized using information from three different sources of evidence. Initially the research team reviewed the iADRS content and mapped onto the model with explicit matches (a direct match between an item and a concept) and/or implicit matches (an indirect/partial match between an item and a concept). Subsequently, the ADCS-iADL items were mapped based on the cognitive sub-domain(s)/concept(s) assigned by the research team using care partners' cognitive debriefing feedback. Finally, research collaborators mapped the ADCS-iADL items to relevant cognitive concepts they thought to be involved with the activity. The findings from all sources were synthesized to get an agreement as to the mapping objectives.

Table 1
Care partners and individuals with AD demographic information ($n = 25$).

	Individuals with AD Summary		Care Partner Summary	
	N	%	N	%
Age groups				
55–64	3	12	–	–
65–74	15	60	–	–
75–85	7	28	–	–
Diagnosis (COD)				
MCI due to AD	7	28	–	–
Dementia due to AD	18	72	–	–
MMSE/MoCA scores				
20–23 (MMSE), 13–17 (MoCA)	6	24	–	–
24–27 (MMSE), 18–23 (MoCA)	13	52	–	–
28–30 (MMSE), 24–30 (MoCA)	6	24	–	–
Sex				
Male	13	52	10	40
Race				
White/Caucasian	15	60	17	68
Black/ African American	4	16	4	16
Native Hawaiian/Other Pacific Islander	3	12	3	12
Other	3	12	1	4
Education				
High school graduate	14	56	1	4
Some college	5	20	4	16
Associate degree	2	8	5	20
Bachelor's degree	2	8	10	40
Master's degree	1	4	4	16
Not reported	1	4	1	4
Employment				
Working part time	0	0	6	24
Working full time	0	0	2	8
Retired	25	100	7	28
Homemaker	0	0	9	36
Not employed due to other reasons	–	–	1	4
Relationship to individual with AD				
Child	–	–	13	52
Partner/spouse	–	–	9	36
Other relative	–	–	3	12

Abbreviations: AD, Alzheimer's disease; COD, Confirmation of diagnosis; MCI, Mild cognitive impairment; MoCA, Montreal cognitive assessment.

3. Results

3.1. Literature review

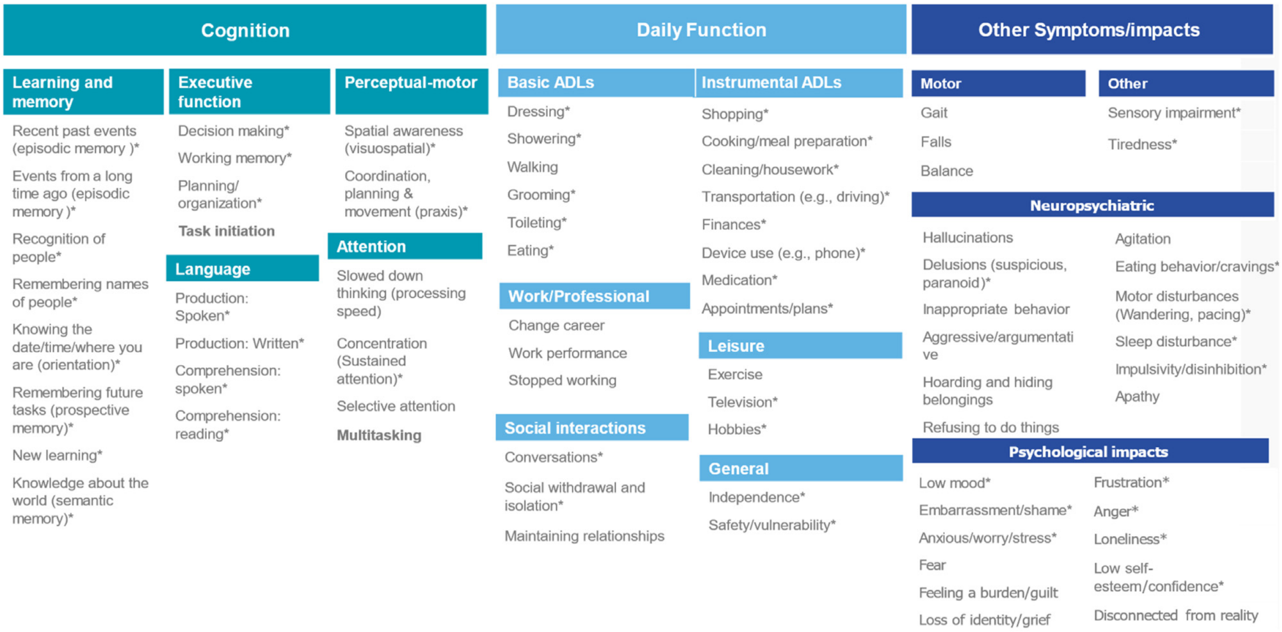
The PubMed search identified a total of 1682 articles for screening. Title and abstract review identified 412 papers warranting full-text review, of which 60 articles were deemed eligible. Of these, 47 included dementia patients, 1 included both dementia and MCI patients, 1 described patients as MCI/AD (which was interpreted as MCI due to AD) and 11 did not explicitly state MCI/dementia (e.g., sample described as mild to moderate AD).

3.2. Sample

A total of 26 care partners took part in this study. One interview was excluded from the analysis due to suspected non-AD dementia (frontotemporal dementia) in the individual described. The mean age of care partners was 52 years (standard deviation (SD) 11) (range 35–70), and the mean age of the individuals with AD was 72 years (SD 6) (range 62–84). See Table 1 for full care partners and individuals with AD demographics. In terms of target recruitment quotas set for the individuals with AD (i.e., age, sex, ethnicity, education, and AD severity), all quotas were met apart from one age group (55–64).

3.3. Concept elicitation

Data from the literature and care partner interviews yielded three overarching domains: Cognition, Daily function, and Other symp-



Cognition

Learning and memory
- Recent past events (episodic memory)*
- Events from a long time ago (episodic memory)*
- Recognition of people*
- Remembering names of people*
- Knowing the date/time/where you are (orientation)*
- Remembering future tasks (prospective memory)*
- New learning*
- Knowledge about the world (semantic memory)*

Executive function
- Decision making*
- Working memory*
- Planning/ organization*
- **Task initiation**

Language
- Production: Spoken*
- Production: Written*
- Comprehension: spoken*
- Comprehension: reading*

Perceptual-motor
- Spatial awareness (visuospatial)*
- Coordination, planning & movement (praxis)*

Attention
- Slowed down thinking (processing speed)
- Concentration (Sustained attention)*
- Selective attention
- **Multitasking**

Daily Function

Basic ADLs
- Dressing*
- Showering*
- Walking
- Grooming*
- Toileting*
- Eating*

Work/Professional
- Change career
- Work performance
- Stopped working

Social interactions
- Conversations*
- Social withdrawal and isolation*
- Maintaining relationships

Instrumental ADLs
- Shopping*
- Cooking/meal preparation*
- Cleaning/housework*
- Transportation (e.g., driving)*
- Finances*
- Device use (e.g., phone)*
- Medication*
- Appointments/plans*

Leisure
- Exercise
- Television*
- Hobbies*

General
- Independence*
- Safety/vulnerability*

Other Symptoms/impacts

Motor
- Gait
- Falls
- Balance

Other
- Sensory impairment*
- Tiredness*

Neuropsychiatric
- Hallucinations
- Delusions (suspicious, paranoid)*
- Inappropriate behavior
- Aggressive/argumentative
- Hoarding and hiding belongings
- Refusing to do things
- Agitation
- Eating behavior/cravings*
- Motor disturbances (Wandering, pacing)*
- Sleep disturbance*
- Impulsivity/disinhibition*
- Apathy

Psychological impacts
- Low mood*
- Embarrassment/shame*
- Anxious/worry/stress*
- Fear
- Feeling a burden/guilt
- Loss of identity/grief
- Frustration*
- Anger*
- Loneliness*
- Low self-esteem/confidence*
- Disconnected from reality

Fig. 1. Conceptual model of AD.
Legend: This figure shows the conceptual model of the patient experience of AD. * = Literature review concept endorsed in interviews. Bold = New concept from interviews. Abbreviations: AD = Alzheimer's disease; ADL = Activities of daily living.

tom/impacts. The consolidated conceptual model is presented in Fig. 1. A total of 22 concepts related to cognition, 25 concepts related to impact of the disease on daily function, and 28 concepts related to other symptoms/impacts were identified across the AD continuum (Table 2). Concepts identified in the literature and endorsed during the interviews and the new concepts reported during the interview reflect concepts more relevant to early symptomatic AD. There was good overlap between the concepts found in the literature and those described during the qualitative interviews, albeit with minor differences.

3.3.1. Cognition

The patient experience of early symptomatic AD was characterized by difficulties in cognitive functioning across 5 sub-domains: learning and memory, attention, executive functioning, language, and perceptual-motor. As expected, care partners typically did not explicitly use these clinical terms.

Within the learning and memory sub-domain, difficulties included memory for recent past events, events from long time ago, recognition of people, remembering names of people, orientation, prospective memory, new learning, and knowledge about the world. Most care partners provided examples indicating impairment in episodic memory (with forgetting recent conversations and misplacing items being frequent issues), orientation (e.g., forgetting the year/month/date/day), and prospective memory (e.g., forgetting upcoming social events or appointments). Care partners were able to make distinctions between forgetting things that happened recently (in the short term), as opposed to memory of events when the person living with AD was considerably younger.

Care partners also highlighted difficulties with aspects of executive functioning, including decision-making, working memory, planning/organization, and task initiation. Care partners often reported the person living with AD had difficulties with working memory (e.g., losing train of thought in conversations or forgets to put sugar/creamer in tea). Within the perceptual-motor sub-domain, areas of concern included difficulties with visuospatial functioning (e.g., navigating and getting lost) and praxis (e.g., needing help with steps or buttoning incorrectly). Within the attention sub-domain, care partners described difficulties with concentration (sustained attention), slowed down thinking (processing speed), selective attention, and multitasking. Finally, within the language sub-domain, care partners noted the people living with AD struggle with both language production, including generation of both spoken and written language, and with language reception, including understanding of spoken language and reading comprehension. All the cognitive concepts identified in the literature were also mentioned by the care partners of individuals with early symptomatic AD with the exception of slowed down thinking and selective attention. Two cognitive concepts not identified in the literature but discussed during the interviews by one care partner each were multi-tasking and task initiation.

3.3.2. Daily function

The daily function overarching domain comprises six sub-domains: basic ADLs, instrumental ADLs, work/professional, social interactions, leisure, and general.

Data incorporated in the basic ADL sub-domain and endorsed during the interviews related to dressing, showering, grooming, toileting or eating concepts, whilst instrumental ADLs concepts related to daily activities beyond the basic ADL such as activities related to shopping, cleaning/housework, cooking/meal preparation, transportation, finances, device use, medication, and appointments/plans. Most care partners provided examples indicating the individual with AD had difficulties with cooking/meal preparation (e.g., needing reminders or supervision whilst cooking), appointments/plans (e.g., forgetting or needing reminders with appointments/plans) and transportation (e.g., no longer able to drive or gets lost driving).

Care partners also shared issues related to leisure activities (such as television and hobbies) and social interactions (for example having conversations, social withdrawal and isolation). Finally, under the general sub-domain, care partners discussed independence (e.g., loss of independence or feeling uncomfortable leaving the individual with AD alone) and concerns with safety/vulnerability (e.g., individual with AD not being safe to be left alone or needing to be watched/accompanied to ensure safety).

Daily function concepts that were identified in the literature but not reported by care partners were maintaining relationships, walking and exercise, as well as all concepts under the work/professional sub-domain.

Table 2
Care partner quotations and the link between cognition and daily function (*n* = 25).

Cognition sub-domains and concepts	Spontaneously reported n (%)	Reported only when probed n (%)	Examples of the link between cognition and daily function provided by care partners	Example quotations
Learning & memory				
Recent events (episodic memory)	23 (92 %)	–	• Forgets where the car is parked • Forgets that they've already had breakfast • Forgets recent conversations • Forgets already watched TV program • Forgets they've already taken medication • Forgets where they put something (misplacing things) • Forgets already done a task • Thinks has already had a shower but hasn't • Thinks needs to go to the store but doesn't • Forgot that no longer driving • Forgets that has AD • Forgets where things are located at home (e.g., location of kitchen items) • Forgot somebody's phone number	• "Do you remember where we parked the car?" The memory is more of the immediate day situations short-term, not long-term" (US-03) • "Like I said, she gets frustrated where certain stuff is. The baking soda, the flour, and it's where it's always been. I've never changed anything." (US-02)
Events from a long time ago (episodic memory)	1 (4 %)	–	• Can't remember the countries she's been to	• she likes to say that she likes to go travelling, and where she's gone to travel and the country she… she struggles on the country names, exactly where she's been. And so, we want to help her. We bring out that photo album and say, "These are the places we all went together," and we'll show the pictures we all took with her at different destinations. INTERVIEWER: How does she respond to that? US22: At first, she's surprised. She's like, "Are you sure this is me, you're not confusing me with somebody else?" (US-22)
Recognition of people	5 (20 %)	–	• Forgetting people met before • Recognition of family • Doesn't remember someone that care partner has known for a long time • Confuses cousin with son • Speaks to people he doesn't know and not to ones he does know	• She sometimes forgets who we are, like her children (US-22) • "Hello" to somebody and he'll say, "Oh who was that?" "Well, it's somebody that I knew from a long time ago." He wouldn't even remember. (US-21)
Remembering names of people	7 (28 %)	1 (4 %)	• Mixes up names of family • Forgets name of someone known for a long time • Can't remember names of new neighbours despite has been told numerous times	• "and she may actually have forgotten someone's name that I know she should have known because she's been knowing them for years" (US-02) • "We have new neighbours two months ago, and we've talked to them so many times, like "Hello", what have you, and introduced to them. She still cannot remember their names and we've been told the names ten times. So, it's like she cannot remember if it's really relatively new or something that's a change. She said to me many times now, "Isn't that [neighbour's name] that lives there" and I've said, "No they moved, that's not [neighbour's name], so things like that." (US-06)
Knowing the date/time/where you are (orientation)	9 (36 %)	12 (48 %)	• Doesn't know year/month/date/day • Forgot that it was Christmas day, their birthday • Doesn't know where they are • No perception of time (of daytime or nighttime)	• "The only thing is, she likes certain days to have certain things. Sometimes she might mix up the day, or what day it is, but, like I said, I can do that. She likes spaghetti on Wednesday. Don't ask me why, [laughs]. Meatloaf Fridays, stuff like that. And she might say, "Is it meatloaf Friday?" I say, "No, Ma, it's only Thursday," stuff like that." (US-13) • "Sometimes I think getting in a new environment is what can trigger the memory. So, all of a sudden, you're in a new place, "Oh my god, where am I? I forgot where I am," kind of things." (US-03)
Remembering future tasks (prospective memory)	11 (44 %)	4 (16 %)	• Forgets upcoming events/needs to be reminded i.e., social events, appointments • Forgets to take the bins out • Forgets to take medication • Needs reminding when TV shows are on • Forgets to make dinner reservation	• "But what happened was, she was forgetting doctor's appointments, which wasn't like her. And that's when I said, "Well, what's happening with this?" And she was trying to act like, "Well, it's not…" but when she missed two or three of them, I said, "No, we need to deal with this," because it's not like her at all." (US-13) • "I make sure I remind her favourite shows are on, on Television, and stuff like that" (US-08)

(*continued on next page*)

Table 2 (*continued*)

Cognition sub-domains and concepts	Spontaneously reported n (%)	Reported only when probed n (%)	Examples of the link between cognition and daily function provided by care partners	Example quotations
New learning	–	4 (16 %)	• Doesn't learn as well • Difficult to learn anything new • Learning technical stuff	• "she doesn't learn as well, so it's more time consuming and just it feels like you're just sat there with lot of redundancy." (US-08) • "So, learning new things, he doesn't retain much information if it's a new thing. It's all about adjusting, like trying to pitch him and trying to find a way where he can retain certain information that is very beneficial. Like to make sure to go to the bathroom, he needs to go shower. Little routines that need to be done every day." (US-10)
Knowledge about the world (semantic memory)	1 (4 %)	–	• Identifying objects	• "And she seems to have a problem now identifying objects" (US-102)
Executive function				
Decision making	–	4 (16 %)	• Care partner in charge of decisions • Can make decisions but apprehensive, unsure, vacillating	• "At this point, I'm in charge of decision making, but I always ask for his opinion anyway" (US-07) • "I make all the pertinent and critical decisions, like all the banking and stuff like that and take care of finances." (US-02)
Working memory	19 (76 %)	3 (12 %)	• Forgets what they're talking about during a conversation • Repeats same questions in a conversation • Losing train of thought in conversations • Forgets instructions • Forgets name of someone just met • Following steps when cooking: May miss a step or ask care partner the next step • Forgets to put sugar/creamer in tea • Forgets if added salt to meal • Forgets laid clothes out to wear within a minute • Forgets to turn off stove • Remembers half of what read in newspaper • Forgets what task he's doing • Doesn't finish tasks started (e.g., take clothes to washing machine and forgets to put wash on) • Forgets to buy something from store • Forgets to take cell phone and keys out with them • Forgets what they are watching	• "he'll be mid-sentence and have to stop because he can't remember his train of thought." (US-17) • "He likes boiled eggs, and he put it on and… it's boiling, but there's no eggs in there. It's like, "Well, the eggs is on the…" it's boiling, and I was like, "Are you boiling water?" He's like, "No, I have some eggs in it." "Well, you forgot to put the eggs in there." (US-23)
Planning/organization	–	10 (40 %)	• Care partner deals with planning • Only planning immediate stuff, not beyond tomorrow • Plans aren't detailed/defined • Less planning (could be due to retirement)	• "No, he doesn't plan anything ahead. I'm the one that tells him whats going to happen, like We're going to see your doctor or We're going to see a cousin." (US-10) • "The only planning she does is immediate stuff like, "I want to go to the Trader Joe's store and shop." But there's no real planning ahead in terms of setting up dates in the calendar or anything like that, it's day-to-day. So, she may want to do something, she brings it up that day. She may mention that she wants to go to Trader Joe's tomorrow, but beyond tomorrow, I don't think there's much planning." (US-102)
Task initiation	–	1 (4 %)	• Can't start a task	• "No, not necessarily. I haven't really seen any of that. It's more like he either can or he can't even begin to do something, per se, when he's having an episode. He either just can't do it or figure out where things are. So, either does or he doesn't. There's no, he'll start it and mix things up or anything. I haven't seen that" (US-05)
Language				
Production: Spoken	7 (28 %)	6 (24 %)	• Struggles to find words to say • Struggles verbalising • Perseveration • Saying things that don't make sense • Slower speech • Echolalia	• "he doesn't talk like he did before. He's very slow. Not the way he used to talk before" (US-10) • "And another thing with the aphasia, is she has echolalia, where she will repeat exactly what she saw or heard." (US-102)

(*continued on next page*)

Table 2 (*continued*)

Cognition sub-domains and concepts	Spontaneously reported n (%)	Reported only when probed n (%)	Examples of the link between cognition and daily function provided by care partners	Example quotations
Production: Written	1 (4 %)	–	• Writing disjointed	• "Her writing is – and I could show you samples of her writing – it's totally disjointed" (US-102)
Comprehension: Reading	2 (8 %)	–	• Recognition of words • Understanding instructions - measurement and temperature incorrect when baking	• "she had 85 % capacity in terms of the occupational therapy capabilities, including primarily referencing the verbal and written skills, and the recognition of words. And now she's at 40 %, and so she said there's been a tremendous deterioration" (US-102) • "Difficulty with measurements. How much flour you put in the measuring cup. Sometimes she overdoes it, but she still has an overview of what goes together to bake an apple pie. I'll make sure that the temperature is correct. She may say "Well I need to put this on 375° Fahrenheit" and I'll look at her instructions where it says 350 and I'll say "Mom, you've gotta leave it at 350 and not 375″ (US-02)
Comprehension: Spoken	3 (12 %)	–	• Cannot grasp word connections/sequences • Misinterpretation of instructions • Losing track of what people are saying	• "and then all of a sudden she may struggle in communicating, where she might be a little hesitant or there might be pauses where she can't grasp certain word connections or sequences" (US-02) • "I think it's because he is losing track of what people are saying. He can't focus on words. He can't calculate what's going on and how it's going on" (US-14)
Attention				
Concentration (Sustained attention)	3 (12 %)	5 (20 %)	• Zones out and forgets what doing (during watching TV, conversations, reading) • Loses interest in conversation and walks away • Changes topics in conversation • Mind wanders	• "he has moments where he's just lost. He'll be watching something or trying to read and he just seems to just zone out and totally forget what's going on or maybe just sleep" (US-05) • "Yes, most of the time he does. Maybe we're talking about one of the car wash places and then he'll start talking about what we did last Christmas. It's like sometimes his mind wanders. (US-10)
Multitasking	–	1 (4 %)	• Multitasking - Talking and watching TV	• "I think she's not as good at doing multi-tasking. It takes her more time to do something like that, talk and watch television. Maybe, she's not as fast as she was." (US-08)
Perceptual-motor				
Spatial awareness (visuospatial)	5 (20 %)	4 (16 %)	• Sense of direction, navigating and getting lost • Mistakes with directions • Got lost finding the bathroom • Forgets direction to home • Dropping things	• "Yes, yes, because we were having instances of him going on routes in driving or even going out and going to the corner store and he would get lost. So, that was another thing that had prompted me to get in touch with the doctor." (US-09) • "I think she has some visual spatial issues, because she seems to be dropping things a lot more" (US-102)
Coordination, planning & movement (praxis)	1 (4 %)	1 (4 %)	• Dressing: buttoned incorrectly • Won't complete a task in order	• "she may have a sweater on and it's not buttoned correctly, it's lopsided" (US-02) • "There's no 1, 2, 3 about it. There's no A, B, C. There's no order in anything. Nothing at all. There's no order. There's no order in the life of an Alzheimer's patient. They can't go from 1 to 2. They'll go from 1 to 9. They'll go from 1 to 8." (US-14)

Daily function sub-domains and concepts	n (%)	Examples of the link between cognition and daily function provided by care partners	Example quotations
Basic ADLs			
Dressing	6 (24 %)	• Clothes don't match • Sweater not buttoned correctly • Misplaces item of clothing • Wears the same clothes • Care partner picks clothes • Forgets to get dressed • Dresses inappropriately for weather • Carer helps with dressing	• "I notice now that she's not colour coordinated, or things aren't matching, or she may have a sweater on and it's not buttoned correctly, it's lopsided." (US-02) • "Just coming out and still hadn't gotten out of his pyjamas, which was never… he would always be dressed" "I have someone that comes in that cleans him… I mean, washes him and helps me get him dressed" (US-14)

(*continued on next page*)

Table 2 (*continued*)

Daily function sub-domains and concepts	n (%)	Examples of the link between cognition and daily function provided by care partners	Example quotations
Showering	4 (16 %)	• Needs prompting/reminding • Forgets to shower • Carer helps wash	• “The main thing is prompting for showering, brushing his teeth, prompting for taking his medicine or any of the things that we take during the day. It’s prompting like, ‘Hey, we need to do this or hey, we have to do that”(US-09) • “I have someone that comes in that cleans him… I mean, washes him and helps me get him dressed “(US-14)
Grooming	3 (12 %)	• Needs prompting • Forgot to brush teeth before having coffee • Forgot to shave • Not wanting to brush teeth	• “The main thing is prompting for showering, brushing his teeth” (US-09) • “Well, he was always very routine, he’s a very routine person, so no… some of the steps are not in order. I have to think about that… Some of the steps are not in order. He does it in different… he would do the same thing every morning… get up, brush his teeth, wash his face, do his hair. Sometimes now he’s going for the coffee and then realise that he didn’t brush his teeth, so that is happening” (US-23)
Toileting	1 (4 %)	• Care partner leads to toilet	• “Well, what he can do is get out of bed. I lead him to the toilet.” (US-14)
Eating	2 (8 %)	• Needs prompts/reminders to eat meals	• “And so, we got to make sure if she does prepare food for herself, she turns off the stove. If she does prepare the food and she puts it on the plate, she remembers to eat it and it’s stuff like that, basically.” (US-22)
Instrumental ADLs			
Shopping	5 (20 %)	• Loses care partner in stores • Doesn’t go alone as would lose sense of direction • Care partner helps them go shopping • Shopping trips are getting longer as patient stops to look at things and read about ingredients	• “Before I used to not have to really keep my eye on her because she would be able to find me, but now it’s getting to a point she is a little bit losing me in the store” (US-04) • “I think our shopping trips keep getting longer. Most of the time, you go to the store and you try to get it done as soon as possible but it’s getting to be like… he wants to go down every aisle. So, it’s extending the shopping trips.” (US-21)
Cooking/meal preparation	14 (56 %)	• Leaving stove on • Care partner keeps an eye on them • Loses self, partway through cooking • Care partner does cooking • Baking affected • Care partner reminds to turn stove off • Care partner reminds left something in microwave • Forgets steps/ingredients when cooking • Support with cooking/meal preparation • Care partner supervises cooking • Care partner gives reminders • Forgets ingredients when cooking • No longer barbeques	• “I wouldn’t want to leave her alone cooking a big meal like that. She’s got a lot of different parts going. My biggest fear is the stove and having the gas left on. It has happened a couple of times” (US-04) • “I think she might miss a step here and there, but I always like to say I’m her professional reminder. I say, “Did you put the salt in?” or “Did you put the sauce?” “Did you do this or did you do that?” And just to make sure that she has done it correct, I’ll just help her cook.” (US-08)
Cleaning/housework	7 (28 %)	• Needing reminders • Support provided for cleaning/housework • Forgets to put thing back in correct place • No longer picks up dirty clothes • Does not fix things in house • Puts things in microwave instead of refrigerator	• “Oh, have you cleaned here?” She might clean the sink, but she might not clean this part. “Oh, did you clean everything?” (US-08) • “He doesn’t pick up his dirty clothes anymore, he just takes his clothes off and just leaves them there. “Honey, you got to go pick up your clothes.” And then I’ve been after him about it too because we’re going to be dog sitting, so that little dog’s going to be coming over here and you know she loves your shoes and socks and, you just got to remember to pick them up” (US-21)

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Table 2 (*continued*)

Daily function sub-domains and concepts	n (%)	Examples of the link between cognition and daily function provided by care partners	Example quotations
Transportation (e.g., driving)	13 (52 %)	• No longer drives • Gets lost while driving • Accident while driving – no longer drives • Care partner does the driving • Stopped being able to drive on freeways by care partner • Reduced driving, no longer comfortable driving	• “Yes, yes, because we were having instances of him going on routes in driving or even going out and going to the corner store and he would get lost.” (US-09) • “That was when she totalled her car, rear-ended somebody, and she could no longer drive” (US-102)
Finances	6 (24 %)	• Care partner takes care of paying bills • Care partner supervises paying bills	• “He doesn’t have any bills. He doesn’t pay, you know like he doesn’t have any other responsibilities. I actually take all the financials and I take responsibility of paying bills and stuff like that.” (US-10) • “Well, I help my mum go shopping, make sure the bills are paid” (US-08)
Device use (e.g., phone)	6 (24 %)	• Difficulty using cell phone • Forgetting computer password • Coffee machine support • Using a coffee machine in a new place • Finds technology challenging • Confusion between phone and remote	• “She’s not able to do it now. (Using cell phone) Or she has a lot of difficulty doing it.” (US-02) • “She no longer really logs onto her computer because she has an issue with trying to enter her password.” (US-102)
Medication	9 (36 %)	• Needs prompting • Forgets already taken medication • Care partner takes care of medication • Smart speaker provides medication reminder	• “Prompting for taking his medicine or any of the things that we take during the day. It’s prompting like, ‘Hey, we need to do this or hey, we have to do that’” (US-09) • “Initially, I let her take the medications herself, and then she started to forget them, or she would double up. So, now I have this… I’ll show you. I have this type of pill case here for her. And now, even with this, sometimes she’ll take it, and I assume she’s taken her medicine, and she’ll forget, or once or twice she doubled up on her medicine.” (US-102)
Appointments or plans	14 (56 %)	• Forgets appointments or plans • Needs reminders about appointments or plans • Needs reminder to look at calendar • Can be late for plans • Care partner accompanies to doctor appointments to write down what is said • Care partner organises schedule • Taken to appointment by care partner	• “For instance, if he knows we’re going for a doctor’s appointment and I… “Oh, can we go into this appointment,” and for example it’s going to be like 12 o’clock, 11 o’clock, and he will forget that he has an appointment. And I just told him maybe an hour ago or maybe two hours ago that you have to be ready because you’re going and leaving for an appointment. He’s forgetting about that.” (US-23) • “He will get dressed, and waiting for his buddy to pass by and pick him up, but like I said he’s personality is… He’s routine, so he will always be ready. Now, he tends to be running late, and he wasn’t running late before. He was very much of a timely person. But because of his forgetfulness… so, if he was supposed to be ready for, say, 7:00am, if I don’t encourage him and I leave him alone to do whatever he wants to do, it’ll be like 7:20 before he gets ready. Before, he’ll be ready probably half an hour early. He was a timely person and very routine. So, because of forgetting times, he forgets what he plans to do” (US-23)
Leisure			
Television	3 (12 %)	• Care partner helps to turn on TV. Can’t activate remote control • Zoning out while watching • Forgets what watching	• “Sometimes, like I mentioned, just getting the TV on” “And in fact, that’s one of the issues that she’s been having recently, is trying to activate the remote.“ (US-102) • “He has moments where he’s just lost. He’ll be watching something or trying to read and he just seems to just zone out and totally forget what’s going on or maybe just sleep” (US-05)

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Table 2 (*continued*)

Daily function sub-domains and concepts	n (%)	Examples of the link between cognition and daily function provided by care partners	Example quotations
Hobbies	3 (12 %)	• Zoning out while reading • No longer attends activities • No longer reads • Going to park or beach	• "He'll be watching something or trying to read and he just seems to just zone out and totally forget what's going on or maybe just sleep" (US-05) • "I think all her intellectual activities have ceased. We used to go to a book club at her Catholic Church once a week." (US-102) • "So, she doesn't read really anymore." (US-102)
General			
Independence	8 (32 %)	• Care partner attends all activities. Not given the chance to be independent • Care partner does not feel comfortable leaving patient alone • Patient wants to do things alone and questions why care partner always there • Loss of independence	• "It's not particularly doing anything to his activities because I am accompanying him on every activity possible. It's just the fact that somebody needs to be there." (US-07) • "Well, like I said I wouldn't quite feel comfortable letting him go out on his own on public transport or go even for a walk because I don't want to take that risk. He might do very well but I just don't want to take that risk." (US-24)
Safety/vulnerability	4 (16 %)	• Not safe to be left alone • Care partner watches/accompanies to ensure safety • Can't go for a walk alone • Care partner keeps an eye on them	• "The challenges is he really forgets about things, that someone is forgetful, it is not safe to be alone or left alone at home. So, to be with that person, to make sure nothing unwanted happens." (US-07) • "We can't let him go for a walk by himself anymore; we have to go with him. We can't take the chance he's gonna wander off, or maybe get hurt or fall down, or get hit by a car or something because he's having one of his moments where he's just completely confused" (US-05)
Social interactions			
Conversations	8 (32 %)	• Can't keep up in conversations • Conversation impact • Struggles in communicating • Takes time to reply	• "It's where he can't even keep up with a conversation or one-on-one conversation, let alone a small group conversation. It's where he's just there. It's like an empty clamshell" (US-14) • "Sometimes she has to think of words to say, and that's a challenge. Sometimes she wants to say things, she doesn't say it, she has to think about it before she… I think she was a little bit more faster, active, reactive rather than now, she takes her time to reply sometimes" (US-08)
Social withdrawal and isolation	2 (8 %)	• Feeling isolation • Limited social interactions • Not wanting to socialize	• "I think she's very cognizant of her verbal deficits, so she's very embarrassed about that and self-conscious about not being able to articulate. So, she passes the phone right back to me. That's an example of the isolation she feels. When we're out walking about and she meets people, again, she'll only say a few words. And for her, I think it's really devastating, because she's a very extroverted individual." (US-102) • "Oh yeah [sighing], I think it's really isolated her, severely limited her social interactions, her daily activities. I think it's probably made her feel very self-conscious and alone. She can't articulate it, but I suspect that." (US-102)

3.3.3. *Other symptoms/impacts*

The conceptual model also included other symptoms/impacts that the individuals with AD may experience, grouped into four sub-domains: motor, neuropsychiatric, psychological impacts, and other. All the sub-domains identified in the literature, except motor, were discussed during the interviews. Regarding the neuropsychiatric sub-domain, the care partners shared neuropsychiatric issues related to delusions, eating behavior/cravings, motor disturbances, sleep disturbances, and impulsivity/disinhibition. Care partners also discussed psychological impacts, such as changes in the individual with AD mood in general, includ-

Table 3
Examples of the relationship between cognitive impairment and the activity covered by each item of the ADCS-iADL.

ADCS-iADL item	Examples of difficulties provided by care partner's	Care partner's perceived relationship to cognitive impairment	Research team decision on cognitive sub-domain(s)/ concept(s)
6a. Selecting clothes when dressing	US-02: Outfits not coordinated, takes longer to dress	Concentration	Executive function
	US-08: Colors don't fit the outfit or clothes not always appropriate for the weather	Cognitive impairment	Executive function
	US-13: Forgets where she put the hat she wants to wear	Cognitive impairment	Memory
9. Conversation	US-02: Gets off topic	Memory and concentration	Working memory, attention
	US-04: Forgets details, does not comprehend full story. Not listening, asks what CP said	Cognitive impairment	Attention
	US-07: On topic but sometimes forgets word related to topic	Memory	Language
	US-08: Goes off topic, forgets what they said	Cognitive impairment	Working memory, attention
	US-09: Goes off topic if there is a lapse in conversation	Memory	Working memory, attention
	US-11: Loses train of thought or direction of conversation	Cognitive impairment	Working memory, attention
	US-17: Word finding difficulty, hard to put words together, loses train of thought mid-sentence	Word finding	Language, attention
	US-102: Non-verbal cues but rarely spoke (2–3 words)	Expressive and receptive aphasia	Language
	US-102: Comprehension issues	Cognitive impairment	Language
	US-19: Might lose train of thought	Memory	Working memory, attention
12. Obtain a hot or cold beverage	US-08: Heats water but then forgets to do the rest	Cognitive impairment: Organization	Working memory
	US-09: Needs prompting if coffee machine not working, wife fills water chamber	Memory	Executive function
	US-102: Perplexed about which coffee to put in the grinder, lack of recognition of familiar objects	Cognitive impairment	Memory
	US-20: Forgets water is on the oven when making coffee	Memory	Working memory
	US-23: Sometimes forgets if distracted, forgets he has already taken milk from fridge	Attention	Attention

Abbreviations: AD = Alzheimer's disease, CP = care partner.

ing issues with low mood, frustration, anger, loneliness, anxiety, embarrassment/shame, and low self-esteem/confidence. Finally, care partners discussed two concepts grouped under the other sub-domain related to sensory impairment and tiredness. Other concepts identified in the literature but not reported by care partners were hallucinations, inappropriate behaviour, aggressive/argumentative, hoarding and hiding belongings, refusing to do things, agitation, apathy, fear, feeling a burden/guilt, loss of identity/grief, and disconnection from reality.

3.3.4. Relationship between cognition and daily function

In recounting the individual with AD experiences with early symptomatic AD, care partners often described interrelated impacts of current and emerging cognitive and functional declines on daily life (Table 2). For example, an individual with AD forgetting about social plans or appointments, forgetting they have taken their medication, forgetting where their car is parked, or remembering to have a shower all reflect the impact of memory impairment on daily functioning.

In some cases, care partners directly cited cognitive difficulties as a reason for imposing pre-emptive restrictions on the individual with AD daily function. Examples of pre-emptive restrictions included not allowing the individual with AD to go shopping alone because they might lose their way (even though this had not yet happened), and not allowing use of the stove due to the potential for harm due to declines in memory and judgment (although no such harm had yet been observed).

Even where care partners reported little to no impact on daily life, the examples they provided (such as misplacing things) reflect the manifestation of cognitive impairment in daily life. Most of the data related to basic ADLs raised in the interviews related to cognitive impairment (as opposed to physical issues or sensory impairment); examples included prompting/reminding to do tasks, with only one care partner noting a carer helps with washing and dressing.

3.3.5. Saturation analysis

Findings supported the comprehensiveness and granularity of the conceptual model related to patient experiences of early symptomatic AD. The saturation analysis indicated three new concepts arising from the last group of interviews: events from a long time ago (episodic memory), eating behavior/cravings, and impulsivity/disinhibition.

3.4. Cognitive debriefing

3.4.1. Relationship between cognitive impairment and the activity covered by each item of the ADCS-iADL

All difficulties that the individuals with AD experienced with activities assessed by the ADCS-iADL items (e.g., shopping, clearing dishes, and dressing) were linked with a cognitive impairment, as explicitly suggested by the care partners (Table 3). Cognitive impairment was the main reason for changes in daily function, with only a few examples where care partners mentioned another issue (e.g., hearing impairment or apathy) as the cause of daily function difficulty.

3.4.2. Relevance of the ADCS-iADL item content and wording, and response options

Difficulties with the activity (or activities) addressed by every ADCS-iADL item were reported by at least one care partner, supporting the relevance of the ADCS-iADL scale in early symptomatic AD. However, some care partners explained that they had taken over the responsibilities queried. In some cases, for instance, the care partner did not allow the individual with AD to attempt an activity (e.g., leaving the home unaccompanied; preparing a hot drink) due to proactive concerns regarding safety, which meant the care partner was limited in their ability to describe the specific difficulties the individual with AD may otherwise have encountered.

Cognitive debriefing analysis indicated some minor issues with relevance, clarity and response options.

Care partners reported that the individual with AD had no difficulties (were independent) for most ADCS-iADL items, except for item 11 (Find belongings) and item 17 (Appointments). The item care partners reported no difficulties the most ($n = 16$) was item 22 (Perform Pastime, Hobby or Game), followed closely by both item 14 (Dispose of Garbage) and item 8a (Select Television Program) ($n = 15$ each).

Care partners most frequently stated that Item 20a (Talk Within 1 h After Reading) ($n = 13$) and item 21 (Most Complicated Things that they Wrote Down) ($n = 11$) were less relevant. For item 20a (Talk Within 1 h After Reading) care partners observed that the individual with AD no longer reads/does not read much or would not discuss their reading material. For item 21 (Most Complicated Things that they Wrote Down),

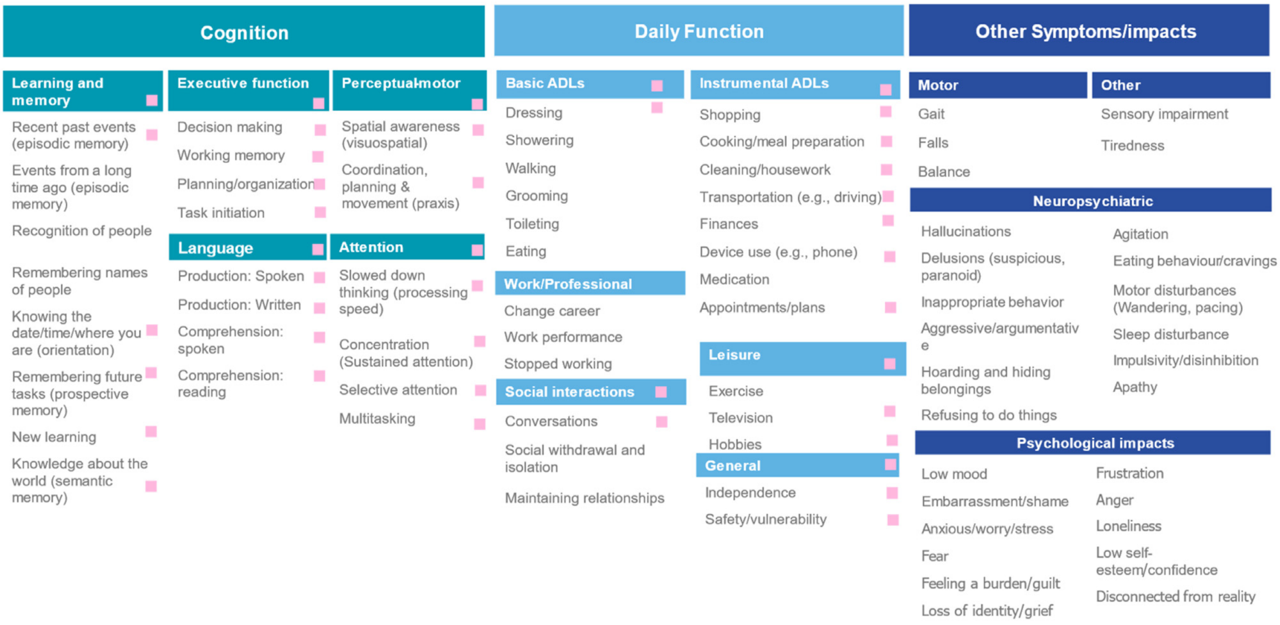

Fig. 2. iADRS concept-to-item mapping.
Legend: This figure shows the concept-to-item mapping of the iADRS to the conceptual model. Concepts with a pink square were covered by at least 1 iARDS item.

care partners noted that the individual with AD did not write things down or they were unsure if they did, with three care partners suggesting that people do not usually write anymore (they use the internet or text).

There were some examples where care partners' responses demonstrated difficulties not explicitly captured by the items or response options; for example, difficulties texting were reported for item 7 (Telephone usage).

There were also some clarity issues identified with the items, particularly item 23 (Use household appliances) where 20 % of care partners felt the phrasing lacked clarity when a single response was needed to characterize functioning across multiple appliances. For item 11 (Find belongings), one care partner queried whether a remote control is considered a personal belonging. Another care partner noted for item 8c (Talk about tv content within a day) the answer depends on if the program was watched before or after AD diagnosis.

Care partner feedback suggested some difficulties when selecting a response option. For example, for item 17 (Appointments), one care partner reported difficulty selecting a response option as none of them applied. For item 7 (Telephone usage), four care partners noted the response options did not typically match the individual with AD experience of using a mobile phone and navigating to their contact list to make calls (e.g., individual with AD does not use white or yellow pages to look up numbers), so they may not choose response option 5 when they are fully independent.

See supplementary Table 4 for full summary of issues.

3.5. Concept-to-item mapping

Fig. 2 depicts a high-level overview of the mapping exercise results.

Regarding the Cognition domain of the conceptual model, each sub-domain ($n = 5$; learning and memory, executive function, language, perceptual motor, and attention) is assessed by at least 1 item of the iADRS. In addition, each of the cognitive specific concepts ($n = 22$; for example, remembering future tasks, decision making, spoken language comprehension, praxis, concentration) is assessed by at least 1 iADRS item with the exception of 3 concepts: events from a long time ago (episodic memory), recognition of people, and remembering names of people.

Regarding the Daily Function domain of the conceptual model, each sub-domain ($n = 6$; basic ADLs, instrumental ADLs, work/professional, leisure, social interactions, and general) is assessed by at least 1 item of the iADRS, except work/professional. At the concept level ($n = 25$; for example, dressing, shopping, change career, hobbies, conversations, independence), 13 of the 25 daily function specific concepts are assessed by at least 1 iADRS item. The specific concepts not covered by the iADRS mainly belong to the basic ADLs and work/professional sub-domains.

Regarding the Other symptoms and impacts domain of the conceptual model, none of the sub-domains ($n = 4$; motor, neuropsychiatric, psychological, and other) are assessed by iADRS items.

4. Discussion

A targeted literature review of qualitative research in AD combined with information gathered through interviews conducted with 25 care partners of individuals with early symptomatic AD identified a broad range of symptoms and subsequent impacts on daily functioning (including bADLs, iADLs, social interactions and psychological impacts) experienced by individuals with AD. This disease experience data was organized into a new conceptual model that provides a basis from which AD outcome measures can be developed or evaluated. The model comprises 75 concepts attributable to three domains: Cognition, Daily Function, and Other Symptoms/Impacts. Care partners interviewed indicated that the individuals they care for (with early symptomatic AD) experience difficulties in cognition, particularly memory of recent events (episodic memory) and daily functioning, including iADLs (such as preparing meals, appointment planning and transportation). These findings align with previous research [4,28]. There was good overlap in the concepts found in the literature (all symptomatic AD stages) and those described during the interviews (early symptomatic AD). Some concepts were not endorsed in interviews likely due to disease stage, for example motor symptoms are more prevalent in later stages of the disease [29,30], whereas other concepts related to working were not mentioned as the sample were retired. Finally, some differences in concepts could also be due to the reporter (i.e., the individual with AD or the care partner), as they are likely to have differing perspectives.

A similar conceptual model, focusing on the patient experience of mild AD was developed by Hartry et al. [31] based on qualitative literature and input from a steering committee of AD experts. While the models have several concepts in common, there is some variation in assignment/categorization of shared concepts. For example, while 'decision-making' falls within the cognition domain in the current model, it is classified as an impact in the Hartry model. In addition, the current model incorporates additional concepts identified through care partner interviews (e.g., understanding written information) that were not included in the previous model. A potential explanation for this, and a strength of the current work was incorporation of specific inclusion criteria (physician-confirmed clinical diagnosis; submission of cognitive test scores) to ensure that care partner interviews reflected experiences of patients and families as the intended stage of disease. In contrast, the studies identified in the literature review rarely provided this confirmation.

The conceptual coverage of the iADRS was evaluated against the new conceptual model. The concept-to-item mapping exercise provided strong evidence supporting the content validity of the iADRS in early symptomatic AD population. All sub-domains of Cognition and Daily function included in the conceptual model are captured by the iADRS, apart from "work and professional life", which is a less generalizable sub-domain. Notably, the concepts not covered by the iADRS included those typically assessed by standalone instruments (i.e., neuropsychiatric symptoms) or less relevant to early-stage AD population of interest (for example, bADLs). Despite the strength of the iADRS in providing overall coverage of concepts, there are specific concepts it does not cover (e.g., recognition of people and remembering their names), which may also be of interest in early symptomatic AD; as well as concepts related to basic ADLs could be considered if the iADRS were to be used in later stages of AD. The findings from the current mapping exercise align with the work by DiBenedetti et al. [17], who reported that the iADRS has the best conceptual coverage amongst other COAs commonly used in AD clinical trials.

The value of integrating measures of instrumental daily functioning with sensitive cognitive tests is supported by prior research describing the relationship between cognitive changes and the rate of functional decline throughout AD continuum [32]. Findings from concept elicitation and cognitive debriefing interviews highlighted the intrinsic connection between experiential declines in cognition and daily function, confirming the contribution of both to the overall patient experience of early symptomatic AD. During concept elicitation, when care partners spontaneously recounted the individual with AD experience, their responses intermingled descriptions of disease-related changes in cognition and daily function, providing evidence of their close link. This confirmed the importance of assessing daily functioning in addition to cognitive functioning in an early symptomatic AD population. Furthermore, during cognitive debriefing of the ADCS-iADL items, care partners clearly described that cognitive impairment was the primary cause for changes in daily function. These results reinforce the relevance of integrating the two scales of cognition and daily function into a single measure of global disease severity.

During cognitive debriefing, minimal issues were raised concerning relevance, clarity, or the response options. The results do, however, provide some suggestions to changes regarding wording or guidance for some ADCS-iADL items, if updates to the scale were to be made. For example, item 11 (Find belongings) and item 23 (Use household appliances) could benefit from clarification or inclusion of subitems to provide more nuanced assessment of abilities in these areas. In addition, some iADL items (item 22- Perform Pastime, Hobby or Game; item 8a- Select Television Program) were considered less relevant for individuals in the early stages of symptomatic AD. Finally, care partners indicated that some items (e.g., item 21- Most Complicated Things that they Wrote Down) were outdated and could be updated to assess more relevant activities and modes of communication (e.g., internet use, direct messaging, texting etc.).

Despite the mentioned strengths of this work, it is important to acknowledge some limitations. Firstly, it is possible that some otherwise eligible and relevant articles may have not been identified through the targeted literature review methodology employed. Secondly, omission or lack of consistency in reporting of AD clinical staging (MCI, mild AD etc.) is a common issue in the current literature. It is therefore not always possible to classify, with certainty, those concepts identified from the literature that are of particular relevance in early symptomatic AD. Finally, although there were attempts to increase sample diversity, the study is limited by geographic and ethnicity bias as all care partners were recruited from the US, all interviews were conducted in English and the sample was predominately white. Further research in a more diverse population would help to corroborate the findings and potentially add additional nuance to the conceptual model.

5. Conclusion

Results from a qualitative literature review and from interviews conducted with current care partners informed the development of a new conceptual model reflecting the patient experience of early symptomatic AD. This patient-centered model integrates concepts of disease-related changes in cognition, daily functioning as well as other areas like motor, neuropsychiatric, and psychological aspects. The concept-to-item mapping exercise showed that the iADRS thoroughly covers both the cognitive and daily functioning concepts included in the conceptual model. These findings strongly support the content validity of the iADRS in early symptomatic AD.

In addition, findings from the qualitative interviews highlight the meaningful and intrinsic connection between disease-related declines in cognition and daily functioning in the patient experience. This emphasizes the importance of an integrated assessment of cognition and function within a single measure of global disease severity. Taken together, the results of this study provide robust, patient-centered evidence supporting the iADRS as a content valid and meaningful COA for use as an endpoint in AD clinical trials.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Compliance with ethics guidelines

Study documents, including the protocol, demographic and health information form, interview guide, screener, and informed consent forms were reviewed by the WCG Institutional Review Board (IRB reference 1,345,864). All care partners provided written informed consent prior to engaging in any study-related procedures. Individuals with AD also provided consent to allow documentation confirming their diagnosis and cognitive test score to be shared during screening. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Care partners were paid a fee in line with fair market value to cover the time taken to participate in the study.

Data availability: The datasets generated and/or analyzed during the current study are not publicly available because they are qualitative transcripts and cannot be completely deidentified.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Laure Delbecque: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Emma Elliott:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Sophie Cleanthous:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Phoebe Heinrich:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Stefan Cano:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Alette M. Wessels:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Alexandra S. Atkins:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100101.

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